



October 22, 2010

**FDA Issues Final Rule on IND Safety Reporting
Also Updates Reporting Requirements for Bioequivalence
and Bioavailability Studies**

For more information, contact:

Mark S. Brown
+1 (202) 626 5443
mbrown@kslaw.com

Pamela Furman Forrest
+1 (202) 661 7888
pforrest@kslaw.com

Beverly H. Lorell, MD
+1 (202) 383 8937
blorell@kslaw.com

Christina M. Markus
+1 (202) 626 2926
cmarkus@kslaw.com

Jessica M. Ringel
+1 (202) 626 9259
jringel@kslaw.com

Elaine H. Tseng
+1 (415) 318 1240
etseng@kslaw.com

**King & Spalding
Washington, D.C.**
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 (202) 737 0500
Fax: +1 (202) 626 3737

San Francisco
101 Second Street
Suite 2300
San Francisco, CA 94105
Tel: +1 (415) 318 1200
Fax: +1 (415) 318 1300

www.kslaw.com

The Food and Drug Administration (FDA) has issued a final rule entitled “Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans.”¹ The final rule is a revision of a proposed rule that was issued in March 2003. The rule amends existing regulations regarding the safety reporting requirements for studies conducted under an investigational new drug application (IND), as well as for bioequivalence and bioavailability studies conducted to support the approval of a generic drug. FDA will issue revisions to the postmarketing safety reporting regulations in a future separate rule. In conjunction with the final rule, FDA also issued a draft guidance document, “Safety Reporting Requirements for INDs and BA/BE Studies,” that describes the new regulations in detail.² The effective date of the final rule is **March 28, 2011**.

Significant Changes from Existing Regulations

Under the final rule, the sponsor must submit an IND safety report to FDA and all investigators to provide notification about each of the following: (1) a serious and unexpected suspected adverse reaction; (2) findings from other studies; (3) findings from animal or in vitro testing, and (4) an increased rate of occurrence of serious suspected adverse reactions. The final rule implements several significant clarifications and modifications to the existing IND safety reporting regulations. FDA highlighted some of these important changes in a press release³ and a Q&A document.⁴ This client alert emphasizes important changes in the regulations related to the reporting requirement, and therefore is not intended to provide a comprehensive discussion of all elements of the final rule. These significant changes include:

- a revision of the terminology used to describe adverse events, serious adverse events, and clarification of how to determine when an investigational drug may be the cause of the serious adverse event and unexpected (*i.e.*, a



FDA & Life Sciences Practice Group

serious and unexpected suspected adverse reaction) , thereby requiring an IND safety report;

- a requirement to report serious suspected adverse reactions that occur at a rate higher than is expected;
- a requirement to report serious suspected adverse reactions that are anticipated within the drug class but not specifically mentioned as occurring with the particular drug under investigation;
- a requirement to report findings from other clinical or epidemiological studies that suggest a significant risk to study participants;
- a requirement to report findings from in vitro testing and clarification of which findings from animal testing must be reported;
- a requirement to report certain adverse drug events that are study endpoints;
- a requirement to report all serious adverse events from bioavailability and bioequivalence studies.

Change in Terminology and Clarification of the Requirement to Report any Suspected Adverse Reaction that is Both Serious and Unexpected

The existing IND safety reporting regulations at 21 C.F.R. § 312.32 use the term “adverse drug experience” to describe adverse events observed during a clinical trial conducted under an IND. The existing regulations require sponsors to file IND safety reports for adverse drug experiences that are both serious and unexpected and “associated with the use of the drug.”⁵ Under the existing regulations, FDA provided little guidance about what adverse drug experiences observed during a clinical trial warranted an IND safety report, and sponsors often reported all serious adverse events, even when there was little reason to believe the serious adverse event was associated with the investigational drug.

Under the final rule, FDA intends to provide greater clarity about which serious adverse events sponsors should report to FDA and investigators. The new regulations eliminate the term “adverse drug experience” and replace it with two terms—“adverse event” and “suspected adverse reaction.” Under the final rule, FDA requires sponsors to file IND safety reports for *suspected adverse reactions that are both serious and unexpected*.⁶

- An “adverse event” is “any untoward medical occurrence associated with the use of drug in humans, whether or not considered drug related,”⁷ that is, any adverse event observed during a clinical trial.
- “Suspected adverse reactions” are a subset of adverse events “for which there is a reasonable possibility that the drug caused the adverse event.”⁸ Per the revised regulations, a “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the



FDA & Life Sciences Practice Group

adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than “adverse reaction”, which means any adverse event caused by a drug.”⁹

- “Unexpected” means an adverse event that is not cited in the investigator brochure or listed at the *specificity or severity* that has been observed. Under the final rule, “unexpected” also means an adverse event that is anticipated within the class of drugs but not specifically mentioned as occurring with the particular drug under investigations.

In addition, the final rule adds a new requirement for reporting *serious suspected adverse reactions that are expected but occur at a rate higher than that listed in the protocol or investigator brochure*. Sponsors must file IND safety reports when they discover “any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.”¹⁰ FDA added this requirement for consistency with ICH guidance.

Sponsors must submit reports no later than 15 calendar days after initial receipt of the information; however, unexpected fatal or life-threatening suspected adverse reactions must be submitted no later than 7 calendar days.¹¹ Under the final rule, FDA provides new instruction that an event may be deemed to be life-threatening by either an investigator or the sponsor.

In the revised regulations, FDA provides three examples of when a serious and unexpected adverse event may be considered causally related to the investigational drug, thereby warranting an IND safety report for a serious and unexpected suspected adverse reaction. First, a single adverse event may suggest a causal relationship when the event is uncommon and known to be strongly associated with drug exposure (*e.g.*, angioedema, hepatic injury, Stevens-Johnson Syndrome).¹² Second, one or more occurrences of an adverse event may suggest a causal relationship when the event is not commonly associated with drug exposure generally, but is nevertheless uncommon in the population exposed to the investigational drug (*e.g.*, tendon rupture).¹³ Third, an aggregate analysis of specific events may suggest a causal relationship when the analysis indicates that the events “occur more frequently in the drug treatment group than in” controls.¹⁴

New Requirement - Reporting of Serious Suspected Adverse Reactions that Occur at a Rate Higher Than Expected

The final rule adds a major new requirement for reporting *serious suspected adverse reactions that are expected but occur at a rate higher than that listed in the protocol or investigator brochure*. Sponsors must file IND safety reports when they discover “any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.”¹⁵ FDA added this requirement for consistency with ICH guidance and the agency’s expectation that the sponsor will track and identify changes in rates of adverse events during the conduct of a clinical trial.



FDA & Life Sciences Practice Group

New Requirement - Reporting of Findings from Other Clinical or Epidemiological Studies that Suggest a Significant Risk to Study Participants

The final rule adds a major new requirement that sponsors file IND safety reports for findings from “other studies” when the findings “suggest a significant risk in humans exposed to the drug.”¹⁶ Other studies include epidemiological studies, pooled analyses of multiple studies (*e.g.*, meta-analyses), and clinical studies other than those conducted under the present IND, and include studies whether or not conducted under an IND and whether or not conducted by the sponsor of the present IND. FDA advises that information from other studies that warrants filing an IND safety report typically would lead to safety-related changes in the protocol, informed consent, investigator brochure, or other aspects of the clinical investigation.¹⁷

Modified Requirement - Reporting of Findings from In Vitro Testing and Clarification of Which Findings from Animal Testing Must be Reported

The existing regulations require IND safety reports for findings from animal testing that suggests a significant risk for humans. The final rule expands this requirement by requiring sponsors to also submit IND safety reports for in vitro testing that suggests a significant risk for individuals exposed to the drug.¹⁸ The final rule clarifies that such findings include reports of mutagenicity, teratogenicity, carcinogenicity, or organ toxicity and that such findings would typically lead to safety-related changes in the protocol, informed consent, investigator brochure, or other aspects of the clinical investigation.¹⁹ Results from studies must be reported whether or not the studies were conducted by the sponsor of the present IND. In the preamble to the final rule, FDA provides additional guidance, noting that findings from animal studies may be reportable, even if they have not been replicated.²⁰ Additionally, a sponsor may be able to determine that a finding of in vitro or animal testing suggests a significant risk for humans before the final study report has been completed.²¹

Reporting of Serious Adverse Events from Bioavailability and Bioequivalence Studies

The final rule adds a new requirement that anyone conducting a bioequivalence or bioavailability study must notify FDA and all participating investigators about *any serious adverse event, whether or not the event is considered to be drug-related*.

Timing and Manner of Reporting

The timing of safety reports is unchanged. Safety reports must be made no later than 15 days after the individual becomes aware of the event, except for fatal and life-threatening adverse events which must be reported no later than 7 calendar days. Although the final rule still requires sponsors to file reports of fatal or life-threatening suspected adverse reactions in 7 days, rather than 15 days, the final rule anticipates electronic reporting and does not narrowly specify that the reports be filed by telephone or facsimile.²² As a change to existing regulations, under the final rule the sponsor *must* submit to FDA any additional information that the agency deems necessary, no later than 15 calendar days after receiving the request.²³



FDA & Life Sciences Practice Group

Additional Important Requirements of the Final Rule

- **Review of all safety information.** FDA still requires sponsors to promptly review all safety information for the drug that is the subject of an IND, including information from domestic and foreign sources, clinical and epidemiological investigations, animal and in vitro studies, published and unpublished scientific literature, reports from foreign regulatory authorities and marketing experience, and from other similar sources.²⁴
- **Safety reporting for studies conducted under an IND when the drug is already marketed in the United States.** The final rule clarifies that sponsors must report suspected adverse reactions observed in a clinical study conducted under an IND even when the drug is already marketed in the United States for another indication or population. The requirement to file an IND Safety Report does not eliminate the postmarketing safety reporting requirements contained in 21 C.F.R. §§ 310.305, 314.80, and 600.80.²⁵
- **Reporting follow-up information.** The final rule eliminates the requirement that sponsors report followup information both within 15 days and in an information amendment or the annual report. The revised regulations only require the 15 day followup report.²⁶
- **Reporting study endpoints.** The final rule also adds the requirement that sponsors report serious and unexpected suspected adverse reactions even if the event may be considered a component of a study endpoint. For example, death from anaphylaxis must be reported, even if a study endpoint is all-cause mortality, when death from anaphylaxis is unexpected and is there is a reasonable possibility that the drug caused the anaphylaxis. Serious and expected suspected adverse reactions that are also study endpoints need not be reported as IND Safety Reports, and must only be reported as described in the study protocol.²⁷
- **Submission of safety reports to all investigators, including those not under a sponsor's IND.** The final rule clarifies that sponsors must submit IND safety reports to all investigators to whom the sponsor is providing drug, including under an investigator's IND (*e.g.*, investigator-sponsored studies) as well as the sponsors' INDs.
- **Investigator reporting requirements.** The final rule changes the investigator reporting requirements. Under the revised regulations, investigators must immediately report to sponsors all serious adverse events, whether or not they events are drug-related, and whether or not they are expected.²⁸ Investigators must also provide sponsors with an assessment of whether there is a "reasonable probability" that the drug caused the event.

Implications of the Final Rule

FDA states in the Federal Register that the final rule will improve the quality of safety reporting, monitor the safety of drug and biological products, and increase the harmonization of safety reporting



FDA & Life Sciences Practice Group

internationally. FDA also believes the final rule will reduce the number of redundant reports. However, it is likely that these changes will require manufacturers to change their policies and procedures regarding IND safety monitoring and reporting. In particular, manufacturers may determine that the final rule will create new expectations for trend analysis of adverse events and processes to determine the significance of potential differences in observed rates relative to those cited in the investigator brochure. To meet the new requirement for IND safety reporting regarding epidemiological studies and pooled analyses of studies, manufacturers will need processes to rapidly determine if the findings “suggest a significant risk in humans exposed to the drug” and ensure that such determinations are credible under FDA scrutiny. Additionally, manufacturers may have to update agreements with investigators regarding the responsibility to report adverse events and adverse reactions. The final rule may also impact the expectations of IRBs regarding safety reports that are to be submitted by investigators.

The final rule is likely to present new challenges regarding “maintaining the blind” in blinded clinical trials. In some situations, in order to determine whether a single adverse event is a serious, unexpected, suspected adverse reaction, the sponsor or investigator may need to break the blind for a patient. FDA notes that what treatment the patient received could “provide critical safety information about the drug that could have implications for the ongoing conduct of the trial (*e.g.*, monitoring, informed consent).”²⁹ However, if patient safety can be assured without unblinding the patient’s information, the sponsor can seek an alternative reporting arrangement from FDA.³⁰ Additionally, if a sponsor anticipates using an alternative reporting arrangement that will maintain the blind, then that arrangement should be described in the study protocol, “including identification of the serious adverse events that will not be reported on an individual basis and the plan for monitoring and reporting results to FDA.”³¹ Alternately, FDA suggests that a Data Monitoring Committee (DMC) could be used to analyze and evaluate unblinded, aggregate adverse events to determine whether the events should be reported as serious, unexpected, suspected adverse reactions. Using a DMC would allow investigators to remain blinded but would potentially greatly expand the responsibilities of many DMCs.³²

King & Spalding will continue to monitor changes to the FDA safety reporting requirements. If you would like help applying these new requirements or updating your policies, procedures or investigator agreements, please contact any of the authors of this client alert.

Celebrating 125 years of service, King & Spalding is an international law firm with more than 800 lawyers in Abu Dhabi, Atlanta, Austin, Charlotte, Dubai, Frankfurt, Geneva, Houston, London, New York, Paris, Riyadh (affiliated office), San Francisco, Silicon Valley, Singapore and Washington, D.C.. The firm represents half of the Fortune 100 and, according to a Corporate Counsel survey in August 2009, ranks fifth in its total number of representations of those companies. For additional information, visit www.kslaw.com.

This alert provides a general summary of recent legal developments. It is not intended to be and should not be relied upon as legal advice.

¹ 75 Fed. Reg. 59935 (Sept. 29, 2010).

² Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>.



FDA & Life Sciences Practice Group

³ FDA News Release, “FDA issues final rule on safety information during clinical trials,” <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227386.htm> (Sept. 28, 2010).

⁴ FDA, Q&A: Final Rule - New Safety Reporting Requirements for Investigational New Drug Applications (INDs), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226365.htm> (Sept. 29, 2010).

⁵ 21 C.F.R. § 312.32(c)(1)(i)(A).

⁶ Revised 21 C.F.R. § 312.32(c)(1)(i) The final rule uses substantially similar but revised and clarified definitions for when an adverse event (or suspected adverse reaction) is considered serious and unexpected. A suspected adverse reaction is *unexpected* if: (1) it is not listed in the investigator brochure; (2) it is listed in the investigator brochure but not with the specificity or severity that is observed; or (3) if it is listed in the investigator brochure as occurring in a class or drugs or as being anticipated from the drug’s pharmacological properties but the event is not specifically mentioned as occurring with the drug under investigation. *See* revised 21 C.F.R. § 312.32(a). When there is no investigator brochure, a suspected adverse reaction may also be “unexpected” if the suspected adverse reaction “is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.” *Id.*

A suspected adverse reaction is considered *serious* if either the investigator or the sponsor determines that the reaction results in: (1) death; (2) a life-threatening adverse event; (3) inpatient hospitalization; (4) prolonging of a current hospitalization; (5) persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; (6) or congenital anomaly/birth defect. Additionally, a suspected adverse reaction may be considered serious if it may jeopardize the patient and may require medical or surgical intervention to prevent one of the preceding outcomes. *See id.*

⁷ Revised 21 C.F.R. § 312.32(a).

⁸ *Id.*

⁹ *Id.*

¹⁰ Revised 21 C.F.R. § 312.32(c)(1)(iv).

¹¹ Revised 21 C.F.R. § 312.32(c)(2).

¹² Revised 21 C.F.R. § 312.32(c)(1)(i)(A).

¹³ Revised 21 C.F.R. § 312.32(c)(1)(i)(B).

¹⁴ Revised 21 C.F.R. § 312.32(c)(1)(i)(C).

¹⁵ Revised 21 C.F.R. § 312.32(c)(1)(iv).

¹⁶ Revised 21 C.F.R. § 312.32(c)(1)(ii).

¹⁷ *Id.*

¹⁸ Revised 21 C.F.R. § 312.32(c)(1)(iii).

¹⁹ *Id.*

²⁰ FDA states: “For example, the agency would not expect a long-term carcinogenicity study to be replicated if findings from the original study suggested significant risk to humans. The validity of the model would be a factor taken into account in evaluating the strength of the evidence of significant risk.” 75 Fed. Reg. 59935, 59949.

²¹ 75 Fed. Reg. 59935, 59950.

²² Revised 21 C.F.R. § 312.32(c)(2).

²³ Revised 21 C.F.R. § 320.31(d)(3).

²⁴ Revised 21 C.F.R. § 312.32(b).

²⁵ Revised 21 C.F.R. § 312.32(c)(4). The preamble to the final rule contains a useful table describing the safety reporting requirements for information generated from clinical studies.



FDA & Life Sciences Practice Group

TABLE 2.—SAFETY REPORTING REQUIREMENTS FROM CLINICAL STUDIES¹

Drug marketed or approved ² in the United States?	Under U.S. IND?	Trial site	Must report to IND?	Must report per post-marketing requirements?
Yes	Yes	U.S. or Foreign	Yes	Yes
Yes	No	U.S. or Foreign	No	Yes
No	Yes	U.S. or Foreign	Yes	
No	No	Foreign		

¹ Areas in the table are left blank when an IND or marketing application would not exist.

² If a drug is approved in the United States, but is not currently being marketed in the United States, the postmarketing requirements would still apply.

²⁶ Revised 21 C.F.R. § 312.32(d). Sponsors should send followup reports to investigators if a suspected adverse reaction “significantly affects the care of the subjects or the conduct of the study.” 75 Fed. Reg. 59935, 59945. Suspected adverse reactions that lead only to minor refinements of the study can be communicated to investigators in a routine update of the investigator brochure, but nevertheless must be sent to FDA as a followup report to an IND safety report.

²⁷ Revised 21 C.F.R. § 312.32(c)(5).

²⁸ Revised 21 C.F.R. § 312.64(b).

²⁹ 75 Fed. Reg. 59935, 59947.

³⁰ *Id.*

³¹ *Id.*

³² *Id.*